



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-094 A(18)

A Phase II Study Of PD0332991 (Palbociclib) in Patients with Advanced or Metastatic Liposarcoma

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

A phase II study of Palbociclib in patients with advanced or metastatic liposarcoma

This is a phase II study of Palbociclib in patients with advanced / metastatic liposarcoma. The primary endpoint is the progression-free survival rate at 12 weeks. Eligible patients must have Rb gene expression by IHC and CDK4 amplification by FISH.

Patients will receive one of two dose schedules:

Schedule 2/1: Palbociclib 200mg given once daily by mouth for 14 consecutive days, followed by 7 days of rest. A cycle will be defined as 21 days.

Schedule 3/1: Palbociclib 125mg given once daily by mouth for 21 consecutive days, followed by 7 days of rest. A cycle will be defined as 28 days.

Re-staging scans will be performed every 6 weeks. Patients continue on study until unacceptable toxicity or disease progression by RECIST.

Following the positive results of the study, a new Expansion Cohort has been added to permit enrollment of up to 20 additional patients. Patients enrolled to this cohort do not require prior treatment with other systemic therapy and do not require Rb expression and CDK4 amplification to be eligible.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objectives

The primary endpoint of this study is to determine the proportion of patients with advanced/metastatic liposarcoma who are progression-free at 12 weeks (PFS, defined as RECIST 1.1 CR + PR + SD) when treated with Palbociclib

2.2 Secondary Objectives

Secondary endpoints include determination of:

- (1) Overall response rate (defined as CR + PR)
- (2) Overall survival
- (3) Clinical benefit rate (CR + PR + SD)



3.0 BACKGROUND AND RATIONALE

3.1 Targeting CDK4 in Liposarcoma

Sarcomas are malignant tumors of mesenchymal origin. Approximately 13,000 cases of soft tissue and bone are diagnosed annually in the US. Liposarcoma, a tumor originating from adipocytes, accounts for more than 20% of soft-tissue sarcoma in adults. Liposarcoma may occur anywhere in the body, but the retroperitoneum and the thigh are the most common sites. Surgery, often with adjuvant radiation therapy for larger tumors, is the mainstay of treatment. Despite primary combined modality therapy, between 30-80% of patients develop recurrent and/or metastatic disease.

The standard of care for metastatic disease for many years has been doxorubicin or a doxorubicin combination. Response rates, however, are low. A recent phase III trial by the EORTC compared doxorubicin to two schedule of ifosfamide in 1st line treatment of metastatic soft tissue sarcomas. This 450-patient trial demonstrated a response rate of just 12% for doxorubicin and 8% for ifosfamide (Lorigan et al., JCO 2007). Another chemotherapy option for metastatic disease is gemcitabine with docetaxel (Maki et al., JCO 2007). This combination shows some activity in other sarcoma subtypes such as malignant fibrous histiocytoma and leiomyosarcoma, but very few patients with liposarcoma respond. Recent phase II studies of the targeted agents imatinib, sunitinib, and sorafenib have shown no responses in liposarcoma. Thus, there is a dearth of active agents for liposarcoma and an unmet medical need.

Palbociclib is an inhibitor of CDK4, a target that is important in the development of well-differentiated and de-differentiated liposarcomas. CDK4 is amplified in 90% of liposarcomas (Sirvent et al., Am J Surg Pathol 2007). Our published gene array data indicates that liposarcomas exhibit an 11.6-fold increase in expression of CDK4 when compared to normal fat (Singer et al., Cancer Research 2007). This makes it one of the highest expressed genes in this tumor type. In liposarcoma cell lines with amplified CDK4 we have shown that shRNAs induce significant apoptosis, suggesting an “oncogenic” addition to this pathway (manuscript in preparation). We have also observed clinical benefit and minor radiological responses in patients with liposarcoma treated on the phase I study of Palbociclib. In particular, we have two patients with metastatic liposarcoma who have had stable disease for 3.1 years (225 mg daily) and 2.3 years (200 mg daily). Notably, the first patient had previously had progression of disease on single agent sorafenib before starting this clinical trial.

Thus the current study is a phase II trial of Palbociclib in patients with liposarcoma. Patients will be followed for time to progression, with the primary endpoint the proportion of patients progression-free at 12 weeks. All patients must have CDK4 amplification by fluorescence in situ hybridization (FISH) on pre-treatment archival tumor tissue. Since intact Rb is required for CDK4 inhibition to be effective, the presence of detectable Rb protein by IHC is also a requirement for study entry. Prior series have shown that the majority of liposarcomas express Rb (eg. 83% in Karpeh et al., Br J Cancer 1995).



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Patients will be treated at the MTD determined by the Phase I study of Palbociclib (O'Dwyer, 2007). Of note, clinical activity was also seen in Rb-expressing germ cell tumors in this study (Vaughn et al, NEJM 2009). Of patients with growing teratoma syndrome, two had prolonged stable disease and one had a partial response.

3.2 Preclinical data on PD 0332991

Palbociclib is an orally administered potent and highly selective reversible inhibitor of Cdk4/6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated in laboratory models. Palbociclib preclinical data indicate that it may be expected to have direct cytotoxic activity as well as potential for growth arrest. Arrest in the G1 phase is known to cause cell death in some tumor types, as demonstrated by this and other G1 arresting agents (eg, Tamoxifen). Moreover, CDK inhibitors like Palbociclib have the potential to enhance the effects of conventional therapies.

Treatment of cultured tumor cells with Palbociclib causes growth arrest that is accompanied by the conversion of phosphorylated Rb to its hypophosphorylated form. Residues serine-780 and -795 of Rb are specifically phosphorylated by Cdk4/6. Consequently, the phosphorylation status of these sites serves as specific biomarkers of Cdk4/6 inhibition by Palbociclib. The IC50 values for reduction of Rb phosphorylation at serine-780 and -795 in MDA-MB-435 breast FDUFLQRPD FH00V ZHUH 0.066 DQG 0.063 μ O. UHVSHFLLYHly. Similar effects on serine-780 and -795 phosphorylation were obtained in Colo-205 colon carcinoma cells. The IC50 values for reduction of Rb phosphorylation are similar to the IC50 values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

In MDA-MB-453 breast carcinoma cells exposed for 24 hours to varying concentrations of Palbociclib, the percentage of cells in G1 began to increase in the presence of as little as 0.04 μ O Palbociclib with a concomitant decrease in other phases of the cell cycle. Maximum HIIHFIV ZHUH DWWOLQHG DI 0.08 μ O.

These data indicate that the 3 biological parameters that are expected for a CDK4/6 inhibitor, growth inhibition, Rb-dephosphorylation, and G1 arrest, all occur in drug-treated cells at comparable concentrations of Palbociclib. This correlation suggests that these biochemical readouts are related and a result of the same mechanism of action (ie, specific inhibition of CDK 4/6).

Time-course experiments indicate that the reduction of Rb phosphorylation begins to occur as quickly as 4 hours after exposure to Palbociclib and reaches a maximum at 16 hours with continued exposure. The inhibition is completely reversible. After removal of the drug, phosphorylation on serine-780 and -795 begins to return in 2 hours and is complete within 16 hours. Active cellular proliferation returns concurrently with Rb phosphorylation. While this suggests that Palbociclib will be most efficacious using continuous daily dosing, intermittent dosing using a variety of schedules has proven as efficacious as continuous daily dosing in animal xenograft models. Tumor regrowth is observed following discontinuation of therapy.



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This provides the basis for chronic intermittent dosing, which allows the integration of other agents as well as a period for recovery from anticipated toxicities, eg, myelosuppression. To determine whether tumors that regressed following discontinuation of Palbociclib remained sensitive to further Palbociclib treatment or whether they had acquired resistance, Colo-205 colon tumors that regressed post Palbociclib treatment were harvested and reimplanted into naïve mice. Following Palbociclib treatment at a dose and schedule identical to the original experiment, the tumors responded with equal sensitivity to the drug and fully regressed, indicating that no resistance had developed during the initial treatment.

Palbociclib exhibits significant antitumor efficacy, including tumor regressions, against multiple human tumor xenograft models in nude mice. In the MDA-MB-435 breast carcinoma PRGH0. IKH 2 GRVH OHYHOV IKDW UHVXOWHG LQ □s0% IXPRU JURZIK LQKLEILRQ VXSSUHVVG phosphorylation on serine-780 over the full 24-hour prior between doses. At 2 lower doses, ZKLFK GLG QRW SURGXFH □s0% IXPRU JURZIK inhibition, phosphorylation returned over the 24-hour prior before the next dose. Similar experiments with the highly sensitive Colo-205 colon carcinoma model show that complete suppression of phosphorylation on serine-780 is not necessary to produce growth inhibition. However, complete suppression of phosphorylation between doses is necessary for tumor regression.

To ensure that Palbociclib acts exclusively by inhibition of Rb phosphorylation, Palbociclib was tested on Rb-negative tumor cells, the MDA-MB-468 human breast carcinoma and the H2009 human NSCLC, both of which have deleted Rb. Palbociclib had no antiproliferative DFWL YLIV RQ IKHVH FHOOV DI WKH KLJKHV FRQFHQWUDILRQ IHVHG (3 3O). ZKLFK LV 1 WR 2 RUGHUV RI magnitude higher than the concentration necessary to inhibit Rb-positive tumor cells. Further evidence that the antitumor activity observed for Rb-positive tumors is due to inhibition of Cdk4/6 was obtained by testing Palbociclib in Rb-negative human tumor xenograft models, the MDA-MB-468 human breast carcinoma and the DU-145 human prostate tumor. Neither tumor responded to Palbociclib .

These findings indicate that Palbociclib is not expected to have an antitumor effect in tumors that do not express Rb, and that only patients with tumor types that express Rb should be included in a clinical trial of Palbociclib .

3.3 Preclinical Toxicity Data

Palbociclib has been examined in various genetic toxicology and safety pharmacology (cardiovascular, neurofunctional, and pulmonary) studies. General toxicology (acute, escalating dose, and 2-week dose range-finding) studies were conducted in rats and dogs. Pivotal toxicology studies were conducted in both species with Palbociclib administered once daily (QD) by gavage for 3 weeks followed by a 1-month reversal period.

The primary Palbociclib toxicities in preclinical studies are to the bone marrow, lymphoid tissues, and testes. These toxicities occurred in both rats and dogs, and are consistent with cell cycle inhibition induced by the intended pharmacology of the drug. Bone marrow suppression resulted in decreases in various hematology parameters; however, the changes were reversible following cessation of dosing. Reversible myelosuppression is anticipated to be dose limiting in man. Palbociclib demonstrated a potential for clastogenicity in the in vitro and in vivo

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micronucleus assays.

Acute intravenous administration of Palbociclib to dogs anesthetized with propofol (a CNS depressant with known respiratory depressant effects) resulted in significant pulmonary effects, including apnea, which were reversible. The effects were transient, appeared related to peak plasma concentrations, and were consistent with centrally-mediated respiratory depression. No changes in pulmonary function occurred in dogs following oral administration of drug.

Pulmonary changes were also observed in rats administered Palbociclib orally. The clinical relevance of these effects, which included rales, dyspnea, and atrophy of tracheal epithelium, is unknown.

Results of the Purkinje fiber and HERG in vitro assays, and cardiovascular study in dogs have indicated a potential for prolongation of the QT interval.

3.4 Clinical toxicity data

A first-in-patient, phase 1, dose-finding study of Palbociclib was conducted in patients with Rb-positive solid tumors or non-Hodgkin's lymphoma (NHL). The primary objective of this trial was to establish the safety profile of Palbociclib and to identify the recommended phase 2 dose of two different treatment schedules. The 3/1 schedule consisted of daily dosing for 21 days followed by 7 days off. The 2/1 schedule consisted of daily dosing for 14 days followed by 7 days off treatment.

A total of 74 patients were enrolled in the study at three sites in the United States and received at least one dose of Palbociclib. The median patient age was 58 years (range 22–78), and the most common primary tumor types were melanoma (n=10; 14%), liposarcoma (n=10; 14%) and colon (n=9; 12%). All but one patient (n=73; 99%) had received any prior therapy, including surgery (n=66; 90%), chemotherapy (n=61; 84%).

In total, 41 patients received Palbociclib on the 3/1 schedule in six different cohorts, with doses ranging from 25 mg QD to 150 mg QD. An additional 33 patients received treatment on the 2/1 schedule in four different cohorts, with doses ranging from 100 mg QD to 225 mg QD.

The MTD for the 3/1 schedule was identified as 125 mg QD and the MTD for the 2/1 schedule was 200 mg QD. The MTD was expanded to 22 patients in the 3/1 schedule and 20 patients in the 2/1 schedule

Myelosuppression was the primary DLT associated with Palbociclib administration. The frequency and severity of myelosuppression for patients treated on both schedules is described in the table below.

Hematologic abnormalities, n (%) [*]	Palbociclib			
	Schedule 3/1 (n=41)		Schedule 2/1 (n=33) Grade 1/2	
		Grade 3/4	Grade 1/2	Grade 3/4
Hemoglobin	22 (55)	3 (8)	21 (64)	1 (3)
Lymphocytes	14 (36)	14 (36)	8 (24)	12 (36)
Neutrophils	21 (54)	8 (21)	14 (42)	8 (24)



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Platelets	18 (45)	0	19 (58)	3 (9)
Leukocytes	27 (68)	9 (23)	22 (67)	7 (21)

The most common treatment-related non-hematologic AEs were fatigue, nausea and diarrhea. Overall, the majority of AEs were mild to moderate in severity (grades 1/2). Nausea was the only grade 3, treatment-related, non-hematologic AE reported on schedule 3/1 (1/41; 2%). Non-hematologic grade 3 events on schedule 2/1 comprised nausea (n=1/33, 3%), vomiting (n=1/33, 3%), hyperglycemia (n=1/33, 3%) and hyponatremia (n=1/33, 3%). No clinically significant ECG changes were observed, and there was no correlation between QTc interval and Palbociclib dose or plasma concentration.

The 2/1 schedule was selected for this phase II trial based on the observed clinical benefit in patients with liposarcoma treated on that schedule (see section 3.1 above).

Preliminary results of the first 20 patients treated on this protocol show that 13 reached 12 weeks without evidence of progression. Thus, the trial met its primary endpoint with an estimated 12-week PFS of 65%, exceeding the 40% required for a positive study. As expected, myelosuppression was the principal toxicity. Of the first 27 patients evaluable for toxicity, the rates of grade 3-4 toxicity were 37% for neutropenia, 15% for anemia, and 33% for thrombocytopenia.

Based on these results, the trial will be expanded to test the 3/1 schedule in patients with liposarcoma. Understanding if there is comparable efficacy will enable the prioritization of which dose/schedule to initially move forward in this indication.

3.5 Pharmacokinetics

Following repeated daily dosing to steady-state Palbociclib was absorbed with a median T_{max} of ~4 hours. The mean PD 0332991 V_z/F was 3103 L, which is significantly greater than total body water (42 L), indicating that Palbociclib extensively penetrates into peripheral tissues. Palbociclib was eliminated slowly; the mean $t_{1/2}$ was 26.5 hours and the mean CL/F was 86.1 L/hour. Palbociclib accumulated following repeated dosing with a median R_{ac} of 2.4, which is consistent with a half-life of ~27 hours.

The major clearance mechanism for Palbociclib is oxidative metabolism catalyzed by CYP3A enzymes. Renal excretion was < 1% of unchanged drug and thus appears to be a minor route of elimination.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II study of Palbociclib in patients with advanced / metastatic liposarcoma. The primary endpoint will be the progression-free survival rate at 12 weeks. Eligible patients must have Rb gene expression by IHC and CDK4 amplification by FISH (except for patients treated in the Expansion Cohort). A one-stage design is used to determine whether patients treated with Palbociclib DFKLHYHG D 3)6 DWH RI □ 40% at 12 weeks.



4.2 Intervention

Patients will receive Palbociclib at one of two doses and schedules:

Schedule 2/1: 200 mg PO daily x 14 days, every 21 days

Schedule 3/1: 125 mg PO daily x 21 days, every 28 days

Expansion Cohort: Dosed as per Schedule 3/1

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Palbociclib (Ibrance) will be supplied commercially by Pfizer, the study sponsor.

5.1 Formulation and Packaging

Palbociclib is formulated in free-based capsules. These capsules come in three strengths and sizes, and all strengths come in 23 count bottles. The sizes and strengths are listed below:

125mg. 0 size capsules – Caramel

100mg. 1 size capsules – Yellow/Caramel

75mg. 2 size capsules – Yellow

Palbociclib may be stored at room temperature and must be protected from light.

5.2 Preparation and Dispensing

Palbociclib is a cytotoxic agent that must be handled and administered with care. Inhalation of drug powder or drug contact with skin and mucous membranes, especially those of the eyes, must be avoided. Should accidental eye contact occur, copious irrigation with water should be instituted immediately followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the exposed area should be irrigated immediately with copious amounts of water for at least 15 minutes. As with other cytotoxic antineoplastic agents, appropriate precautions should be followed in accordance with local guidelines.

5.3 Administration

Oral Palbociclib is administered once daily. On clinic visit days, the patient should wait to take that day's dose until continued treatment on the protocol is approved by the physician. Capsules must be swallowed intact. Due to the lack of stability data and possible hazards associated with topical and environmental exposure to cytotoxic agents, capsules must not be opened and emptied into any vehicle for oral ingestion. Capsules should be taken with food. The absorption and exposure of Palbociclib was very low in approximately 13% of the population under the fasted condition with administration of the free base capsule formulation. Patients should be encouraged to take their dose at approximately the same time each day. However, a variance of up to 12 hours either way is

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allowed for any given dose, rather than miss a day's dose. If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits anytime after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next day's dose of Palbociclib. A study medication diary is to be completed for each dose of Palbociclib.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- 6.1.1 A diagnosis of liposarcoma confirmed at MSKCC. Because myxoid / round cell liposarcoma does not have significant CDK4 amplification, patients with this subtype are not eligible.
- 6.1.2 Metastatic and/or locally advanced or locally recurrent disease that is not surgically resectable, with evidence of disease progression, either clinically or radiographically, as determined by the investigator
- 6.1.3 All patients must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be >10 mm when measured by CT, MRI or caliper measurement by clinical exam; or >20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI.
- 6.1.4 A minimum of 1 prior systemic regimen for recurrent/metastatic disease. Note: This requirement does not apply to patients enrolled in the Expansion Cohort. The last dose of systemic therapy (include targeted therapies) must have been given at least 2 weeks prior to initiation of therapy. Patients receiving BCNU or mitomycin C must have received their last dose of such therapy at least 6 weeks prior to initiation of therapy.
- 6.1.5 Patients with brain metastasis that have been treated with definitive surgery or radiation and have been clinically stable for 3 months are eligible.
- 6.1.6 Age ≥ 18 years.
- 6.1.7 ECOG performance status 0 or 1 (Please see Appendix C for ECOG/KPS conversion table).
- 6.1.8 Adequate organ and marrow function as defined below (ULN indicates institutional upper limit of normal):

Absolute neutrophil count $\geq 1.5 \times 10^9/L$



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Hemoglobin	<input type="checkbox"/> 9.0 g/dL
WBC	<input type="checkbox"/> $3.0 \times 10^9/L$
Platelets	<input type="checkbox"/> $100 \times 10^9/L$
Total bilirubin	<input type="checkbox"/> 1.5 u ULN except for patients with known Gilbert syndrome
AST(SGOT)/ALT(SGPT)	<input type="checkbox"/> 3 u institutional ULN
Serum creatinine	<input type="checkbox"/> 1.5 u ULN or Creatinine Clearance > 50 mL/min (calculated by Cockcroft-Gault method)
QTc interval	<input type="checkbox"/> 470 msec

6.1.9 Patients must not have current evidence of another malignancy that requires treatment.

6.1.10 The effects of Palbociclib on the developing human fetus at the recommended therapeutic dose are unknown. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence). Women must not breast feed while on study.

6.1.11 Ability to understand and the willingness to sign a written informed consent document.

6.1.12 Ability to swallow intact Palbociclib capsules

6.1.13 Patients' tumors must express Rb, as assessed using an historical biopsy sample if available or a new ☐ 1+ staining for Rb (see Section 8.0). Patients' tumors must also have evidence of CDK4 amplification by FISH (see Section 8.0). Note: This does not apply to patients enrolled in the Expansion Cohort.

6.2 Subject Exclusion Criteria

6.2.1. Patients who have not recovered from adverse events of prior therapy to ☐ 1&, CTCAEv4.0 Grade 1.

6.2.2 Patients receiving any other investigational agents.

6.2.3 Patients who have received prior treatment with a selective CDK4 inhibitor

6.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Palbociclib.



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- 6.2.5 Uncontrolled intercurrent illness including, but not limited to, known ongoing or active infection, including HIV, active hepatitis B or C, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (specifically, atrial fibrillation or ventricular dysrhythmias except ventricular premature contractions), or psychiatric illness/social situations that would limit compliance with study requirements.
- 6.2.6 Pregnant women and women who are breast-feeding.
- 6.2.7 Patients with a history of long-QT syndrome or documented family history of long-QT syndrome. Patients who must remain on drugs that prolong the QT interval.
- 6.2.8 Palbociclib is a substrate of CYP3A. Caution should be exercised when dosing Palbociclib concurrently with CYP3A inducers or inhibitors. Furthermore, patients who are taking concurrent medications that are strong inducers/inhibitors or substrates of CYP3A4 should be switched to alternative medications to minimize any potential risk. A list of CYP3A4 substrates, inducers and/or inhibitors is provided in Appendix B. The following medications with strong potential for interaction are not allowed:

indinavir
nelfinavir
ritonavir
clarithromycin
itraconazole
ketoconazole
nefazodone
saquinavir
telithromycin
carbamazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's wort
Troglitazone

7.0 RECRUITMENT PLAN

Both men and women and members of all races and ethnic groups are eligible for this trial. The clinical trial will be listed on the clinicaltrials.gov website as well as on the MSKCC website. Patients will not be paid for participation in this study.

8.0 PRETREATMENT EVALUATION



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An existing tumor biopsy sample or a freshly obtained tumor sample will be used to assess for Rb expression and CDK4 amplification. Both are required for protocol entry. Note: This requirement is waived for patients in the Expansion Cohort because our data has shown that CDK4 amplification is nearly universal, and a future phase 3 study will plan to enroll patients with liposarcoma without requiring CDK4 amplification. CDK4 amplification testing by FISH will be performed in the laboratory of Cristina Antonescu, MD, MSKCC. Rb expression will be determined by immunohistochemistry. Patients' tumors must express Rb DV DVVHVHVG E\ ,+& VIDLQJQJ D D IHYH □ 1+. \$ 1+ VIDLQJQJ IHYH LV HTXLYD IHW IR D PLQLPD intensity level that is nonetheless determined to be above background. Rb staining by IHC will be performed by Alan Meeker, PhD, Johns Hopkins Oncology.

Pretreatment evaluations include:

- x Tumor assessment (either archival tissue or fresh biopsy if necessary) to evaluate for Rb expression and CDK4 amplification
- x Medical history
- x Physical exam
- x CBC w/ plt, diff
- x Serum chemistry
- x Radiologic evaluation (CT or MRI)
- x EKG
- x Blood pregnancy test (for women of child-bearing potential)

Baseline assessments including radiologic evaluation but excluding tumor assessment for Rb expression and CDK4 amplification must be done within 3 weeks of starting protocol therapy.

9.0 TREATMENT/INTERVENTION PLAN

Treatment will consist of either:

Schedule 2/1: Palbociclib 200mg given once daily by mouth for 14 consecutive days, followed by 7 days of rest. A cycle will be defined as 21 days.

Schedule 3/1: Palbociclib 125mg given once daily by mouth for 21 consecutive days, followed by 7 days of rest. A cycle will be defined as 28 days.

Patients may deviate from the study schedule at the Principal Investigator's discretion as long as patient safety is not compromised.

Treatment will be administered on an outpatient basis. Appropriate dose modifications for Palbociclib are described in Section 11.4.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Schedule 2/1:



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Cycle 1, Week 1

- x Physical Exam
- x CBC with platelets, differential
- x Serum chemistry

Cycle 1, Week 2

- x CBC with platelets, differential
- x Serum chemistry

Cycle 1, Week 3

- x CBC with platelets, differential
- x Serum chemistry

Cycle 2 – 12

- x Physical exam at the start of every cycle
- x CBC with platelets, differential at the start of every cycle
- x Serum chemistry at the start of every cycle
- x EKG at the start of every cycle (after Cycle 8 , at the start of every other cycle)
- x CT or MRI every 6 weeks (starting with Cycle 3 Week 1)

Cycle 13+

- x Physical exam at the start of every other cycle
- x EKG at the start of every other cycle
- x CBC with platelets, differential at the start of every cycle
- x Serum chemistry at the start of every cycle
- x CT or MRI every 12 weeks (3 cycles)

Start of each cycle:

- x Adverse events
- x Concurrent medications

Off study: 3-4 weeks after last dose

- x Physical Exam
- x CBC with platelets, differential
- x Serum chemistry
- x EKG

Schedule 3/1:

Cycle 1, Week 1

- x Physical Exam
- x CBC with platelets, differential
- x Serum chemistry

Cycle 1, Week 2

- x CBC with platelets, differential
- x Serum chemistry

Cycle 1, Week 3



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- x CBC with platelets, differential
- x Serum chemistry

Cycle 1, Week 4

- x CBC with platelets, differential
- x Serum chemistry

Cycle 2 – 9

- x Physical exam at the start of every cycle
- x CBC with platelets, differential at the start of every cycle
- x Serum chemistry at the start of every cycle
- x EKG at the start of every cycle (after Cycle 8 , at the start of every other cycle)
- x CT or MRI every 6 weeks

Cycle 10+

- x Physical exam at the start of every other cycle
- x EKG at the start of every other cycle
- x CBC with platelets, differential at the start of every cycle
- x Serum chemistry at the start of every cycle
- x CT or MRI every 12 weeks

Start of each cycle:

- x Adverse events
- x Concurrent medications

Off study: 3-4 weeks after last dose

- x Physical Exam (May be performed by a physician not affiliated with the protocol if patient is unable to return to MSKCC)
- x CBC with platelets, differential
- x Serum chemistry
- x EKG

Any study assessments may be performed + / - 3 days from the scheduled time.

Pre- and post-treatment biopsies may be obtained in at least 10 patients on the study. The biopsy will be used to assess total Rb, phospho-Rb to confirm CDK4 inhibition, induction of apoptosis (781(/ DQG FOHDYHG FDVSDVH 3). DQG PDUNHUV RI FH00XODU VHQHVFHQFH (VHQHVFHQFH ù-galactosidase) and proliferation (Ki67). Other biomarkers may also be explored. In addition, a third biopsy may be performed in patients who are removed from the study for disease progression. This will enable us to better understand mechanisms of resistance to CDK4 inhibition. All biopsies are optional for patients.

Collection of Specimen(s)

The pre-treatment biopsy will be collected within 2 weeks of the first dose. The post-treatment biopsy will be collected after at least 3 weeks of treatment (i.e., after completion of cycle 1). The exact timing of the biopsy is at the discretion of the Principal Investigator.

Patients will also have the option of having a second biopsy within 14 days following removal from study for disease progression.



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Handling of Specimens(s)

For each sample indicate the unique subject ID number, histology diagnosis, and the date of the specimen.

Shipping of Specimen(s): Tumors will be sent to:

Grazia Ambrosini, Ph.D.
Memorial Sloan-Kettering Cancer Center
Sarcoma Laboratory, Z-1841
1275 York Ave
New York, NY 10065
Tel: 646-888-2183
Fax: 646-422-0631
Email: ambrosig@mskcc.org



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Patients will undergo evaluation on treatment according to the tables below.

SCHEDULE 2/1	Pre-Study	Cycle1 Wk 1	Cycle1 Wk 2	Cycle1 Wk 3	Cycle2 Wk 1	Cycle2 Wk 2	Cycle2 Wk 3	Cycle3 Wk 1	Cycle3 Wk 2	Cycle3 Wk 3	Cycle4 Wk 1 +	Off Study ^d
Palbocidib ^a		X	X		X	X		X	X		X	
Tumor for RB and CDK4	X											
Informed consent	X											
Medical history	X											
Concurrent meds	X	X			X			X			X	
Physical exam ^f	X	X			X			X			X	X
CBC w/diff, plts	X	X	X	X	X			X			X	X
Serum chemistry ^b	X	X	X	X	X			X			X	X
EKG	X				X			X			X	X
Adverse event evaluation		X			X			X			X	X
Radiologic evaluation ^e	X	Radiologic measurements should be performed every 6 weeks.										
B-HCG	X ^c											
Tumor Biopsy ^g					X ^g							X ^g

- a: Palbocidib 200mg PO daily x 14 days, every 21 days.
- b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
- c: Serum pregnancy test (women of childbearing potential).
- d: Off-study evaluation 3-4 weeks after last dose.
- e: CT and/or MRI as appropriate based on location of disease. After 36 weeks, radiologic evaluation will be performed every 12 weeks.
- f: After Cycle 13, physical exam will be performed at every other cycle. After Cycle 8, EKGs will be performed at every other cycle.
- g: Both post treatment and off study tumor biopsies are optional.



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SCHEDULE 3/1	Pre-Study	Cycle1 Wk 1	Cycle1 Wk 2	Cycle1 Wk 3	Cycle1 Wk 4	Cycle2 Wk 1	Cycle2 Wk 2	Cycle2 Wk 3	Cycle2 Wk 4	Cycle4 Wk 1 +		Off Study ^d
Palbocidib ^a		X	X	X		X	X	X		X		
Tumor for RB and CDK4	X											
Informed consent	X											
Medical history	X											
Concurrent meds	X	X				X				X		
Physical exam ^f	X	X				X				X		X
CBC w/diff, plts	X	X	X	X	X	X				X		X
Serum chemistry ^b	X	X	X	X	X	X				X		X
EKG	X					X				X		X
Adverse event evaluation		X				X				X		X
Radiologic evaluation ^e	X	Radiologic measurements should be performed every 6 weeks.										
B-HCG	X ^c											
Tumor Biopsy ^g	X ^g				X ^g							X ^g

a: Palbocidib 125mg PO daily x21 days, every 28 days.

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

c: Serum pregnancy test (women of childbearing potential).

d: Off-study evaluation 3-4 weeks after last dose.

e: CT and/or MRI as appropriate based on location of disease. After 36 weeks, radiologic evaluation will be performed every 12 weeks.

f: After Cycle 10, physical exam will be performed at every other cycle. After Cycle 8, EKGs will be performed at every other cycle.

g: Pretreatment biopsy to be collected within 2 weeks of first dose. Both post treatment and off study tumor biopsies are optional.



11.0 TOXICITIES/SIDE EFFECTS

Expected toxicities include

- x Myelosuppression (anemia, thrombocytopenia, leukopenia, lymphopenia, neutropenia)
- x Nausea
- x Vomiting
- x Hyperglycemia
- x Hyponatremia

The severity and frequency observed in the phase I trial of Palbociclib are summarized in section 3.4 above.

11.1 Dose modification for toxicity

Patients who experience dose-limiting toxicity (DLT) may have their dose modified.

A DLT is an adverse event occurring after the initiation of Palbociclib treatment that meets any of the following criteria within a given cycle:

DLT is defined as:

1. *UDGH 4 KHPDWRORJLF IR[FLW\ (LQFOXGLQJ SODWHOIV <2s.000/3/. DEVROXH QHXWURSKLO count >\$1& <s00/3/. KHPRJIRELQ <6.5 g/dL);
2. \$1& <1000/3/ (*UDGH 3 QHXWURSHQLD) DVVRFLDWHG ZLWK D GRFXPHQWHG LQIHFWLRQ RU fever □38.s□&;
3. □ *UDGH 3 QRQKHPDIRORJLF WHDWPHQW-related toxicity, except those that have not been maximally treated (eg, nausea, vomiting, diarrhea) or that the patient considers tolerable, such as skin rash. In an asymptomatic patient, Grade 3 QTc prolongation (QTc >500 msec) will first require repeat testing, manual over-read to exclude confounding factors such as U wave or other abnormal wave forms, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation. If, after correction of any reversible causes, the Grade 3 QTc prolongation persists, then the event should be considered a DLT.
4. Inability to receive the next dose of PD 0332991 within 1 week (±1 day) of the last cycle due WR IDFN RI KHPDIRORJLF UHFRYHU\ (SIDWHWHV <s0.000/3/. \$1& <1.000/3/. DQG hemoglobin <8.0 J/G); RU GXH IR SURORQJHG QRQKHPDWRORJLF IR[FLWLHV RI □ *UDGH 3 severity.

The occurrence of a DLT necessitates immediate interruption of the scheduled study treatment. Resumption of study treatment for patients experiencing DLTs is permitted, contingent on the criteria defined in Section 11.3. For QTc-related DLTs, a risk/benefit assessment by investigator and sponsor will determine whether or not to continue study drug at a reduced dose following return of the QTc interval to baseline.

11.2 Treatment Interruption

Treatment is to be interrupted under the following circumstances:

- DLT (Section 11.1);

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- ☐ *UDGH 3 QRQKHPDWRIRJLF RU KHPDIRIRJLF WR[LFLW (LQFIXGLQJ SIDIHQHV <0.000/3/. \$1& <1.000/3/. DQG KHPRJORELQ <8.0 J/G/) LQ WKH ILUVI F\FH; IRU VXEVTXHQI F\FOHV. DQFLOODU\ supportive medications such as anti-diarrhea agents should be used in order to maintain full dose;
- Dosing may be interrupted or discontinued for serious AEs (SAEs) at the investigator's discretion.

11.3 Recovery Requirements Following Treatment Interruption

Delay retreatment following treatment interruption for toxicity until all of the following conditions have been met:

- ☐ 3ODWHQHW FRXQI ☐ 0.000/3/;
- ☐ \$1& ☐ 1000/3/;
- ☐ +HPRJORELQ ☐ 8.0 J/G/;

• Treatment-UDHWHG QRQKHPDIRORJLF \$(V KDYH UHFRYHUVHG IR ☐ *UDGH 1 RU IR EDVHILQH. ZLWK WKH exception of alopecia;

If treatment interruption results from decline in hematologic parameters, the frequency of blood count assessments should be increased as indicated clinically.

11.4. Dose Adjustments Following Treatment Interruption for Toxicity

Patients who have experienced a DLT must have any subsequent doses reduced once they meet recovery requirements (Section 11.3). Patients who had a dose interruption for an AE that did not meet DLT criteria (eg, Grade 3 hematologic toxicity) are to continue at the same dose of PD 0332991 as administered in the previous cycle.

Schedule 2/1:

Patients resuming treatment following DLT are to have their dose reduced to **150mg**.

If patients require a second dose modification, the dose should be reduced to **100mg**.

Schedule 3/1:

Patients resuming treatment following DLT are to have their dose reduced to **100mg**.

If patients require a second dose modification, the dose should be reduced to **75mg**.

The maximum number of dose reductions is 2. The maximum delay for any reason, including toxicities, is 3 weeks. If study drug is withheld for more than 3 continuous weeks due to a treatment-related toxicity that does not resolve, the patient will be withdrawn from the study.

Subjects will be withdrawn from the study if they fail to recover to CTCAE v4.0 Grade 0-1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 21 days OR they experience agent related adverse events

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requiring dose modification despite two previous dose reductions (i.e. would require a 3rd dose reduction) unless the investigator believes that the subject should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment. Patients requiring dose reductions should not have the dose re-escalated with subsequent treatments.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Measurement of antitumor effect

Patients should be reevaluated for response every 6 weeks (by the clock, not at the end of a specific cycle). After 36 weeks, patients should be re-evaluated for response every 12 weeks. Again, the scans should be performed on schedule, not according to the number of cycles administered. Patients who achieve a complete or partial response should continue to have follow-up scans on schedule to document the duration of the response.

12.2 Parameters of Response – RECIST (version 1.1)

Please refer to the following reference for complete details: Eisenhauer EA, Therasse P, Bogarerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009; 45:228-247.

12.2.1 Measurable disease ("Target") is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≤ 10 mm when measured by CT (CT scan slice thickness no greater than 5 mm*); ≥ 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); and ≥ 20 mm by chest x-ray.

*If CT scan with slice thickness > 5 mm is used, the minimum lesion size must have a longest dimension twice the actual slice thickness.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in **short axis** when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). **At baseline and in follow-up, only the short axis will be measured and followed.**

Clinical lesions will only be considered measureable when they are superficial and ≥ 10 mm diameter as assessed using **calipers** (e.g. skin nodules). When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI may be substituted for contrast enhanced CT for some sites (e.g. for abdomen and/or pelvis), but NOT lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of



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5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness.

Tumors within a previously irradiated field will be designated as “non- target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Bone lesions:

- x Bone scan, PET scan or plain films are NOT considered adequate imaging techniques to measure bone lesions.
- x Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable if the **soft tissue component** meets the definition of measurability described above.
- x Blastic bone lesions are non-measurable.

Cystic lesions:

- x Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable).
- x Cystic lesions thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.2.2 Non-measurable disease (“Non-Target”) is defined as all other lesions, including small lesions (<10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions.

Lesions considered truly non-measurable include:

- x Leptomeningeal disease
- x Ascites
- x Pleural or pericardial effusion
- x Inflammatory breast disease
- x Lymphangitic involvement of skin or lung
- x Abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

12.2.3 Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of **5 lesions total** (and a **maximum of two lesions per organ**) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved



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organs, but in addition should be those that lend themselves to reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the **baseline sum diameters**. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent”. It is possible to record multiple non-target lesions involving the same organ as a single item on the D2M form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should ALWAYS be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.2.4 Response Criteria

12.2.4.1 Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

12.2.4.2 Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking into reference the baseline sum diameters.

12.2.4.3 Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). **In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.** (Note: the appearance of one or more **NEW** lesions is also considered progression. Guidance on when a lesion is to be considered new is provided in the above cited reference). **Unequivocal progression of existing non-target lesions** is also considered progression (a detailed description and examples of unequivocal progression of existing non-target lesions is provided in the above cited reference).

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.



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12.2.4.4 Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.2.4.5 Not evaluable (NE) is when no imaging/measurement is done at all at a particular time point. The patient is not evaluable (NE) at that time point.

12.2.4.6 Early death is defined as having NO repeat tumor assessments following initiation of study therapy resulting from the death of the patient due to disease or treatment.

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be recorded as '**symptomatic deterioration**'. Every effort should be made to document objective progression even after discontinuation of treatment.

Confirmation of response (for both CR and PR): Complete or partial response may only be claimed if the criteria for each are met at a subsequent time point (≥ 4 weeks later) in studies with a primary endpoint that includes response rate. When response rate is a secondary endpoint (e.g. randomized phase II or III studies with progression-free survival or overall survival as primary endpoint) confirmation is NOT required.

Special note on lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Special note on target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the D2M form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a **default value of 5 mm** should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well).



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12.2.5 Evaluation of best overall response is according to table below:

Time point response : patients with target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

12.2.6 Duration of response is defined as the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study).



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12.2.7 Duration of stable disease is measured from the start of the treatment (in randomized trials, from the date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

12.2.8 Progression-Free Survival is the period from study entry until recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study), death or date of last contact.

12.2.9 Survival is the observed length of life from entry into the study to death or the date of last contact.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease he/she will be taken off study and referred for alternative therapy.

If at any time the patient develops unacceptable toxicity he/she will be removed from study.

If the patient is unable to follow the requirements of the protocol for treatment or evaluation he/she will be removed from study.

14.0 BIOSTATISTICS

The primary endpoint of this study is to determine the progression-free survival at 12 weeks for patients with liposarcoma treated with Palbociclib. Progression includes both disease progression (as defined by RECIST 1.1) and death from any cause. Based on historical controls (Van Glabbeke et al. Eur J. Cancer 2002; 39:543-549), a PFS of > 40% at 3 months is considered promising for second-line therapy, and a PFS of < 20% is considered not promising.

A one-stage design will be used. Accrual will continue until 28 evaluable patients have been treated. The study will be claimed to be positive if there are 9 or more who are progression-free at 12 weeks. This design has a type I error rate of 0.09 and a type II error rate of 0.15. The probability of claiming the study positive given various true rates of 12-week PFS is given as follows.

True Rate of PFS at 12 weeks	Probability of Claiming the Study Positive
0.2	0.09
0.3	0.47
0.4	0.85
0.5	0.98
0.6	>0.99

The study met its primary endpoint for patients treated on the 2/1 schedule. The estimated PFS at 12 weeks is 66% (Dickson et al., JCO 2013, in press). The study was expanded to enroll an additional 28 patients to be treated on the 3/1 schedule. The 3/1 schedule will also be evaluated using a one-stage design. Given the high PFS rate observed on the 2/1



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schedule, the 3/1 schedule will be held to a higher standard. An acceptable 12 weeks PFS rate will be 60% and an unacceptable rate will be 35%. The 3/1 schedule will be claimed positive if there are 14 or more who are progression free at 12 weeks. This design has a type I error rate of 0.07 and a type II error rate of 0.10. The probability of claiming the study positive given various true rates of 12-week PFS is given as follows.

True Rate of PFS at 12 weeks	Probability of Claiming the Study Positive
0.3	0.02
0.35	0.07
0.4	0.19
0.5	0.57
0.6	0.90
0.65	0.97
0.7	0.99

The 3/1 schedule also met its primary endpoint (to be reported at ASCO 2013). Based on these results, a phase 3 study of the 3/1 schedule is planned. In the interim, the current study will be expanded to include up to 20 additional patients in the Expansion Cohort. No formal statistical hypothesis is being tested in the Expansion Cohort however the outcomes will be reported with descriptive statistics as described in the next paragraph.

Secondary endpoints include determination of RECIST overall response rate (CR + PR), clinical benefit rate (CR+PR+SD) and overall survival. Response rate and clinical benefit rate will be estimated with the confidence interval provided. PFS and the overall survival probabilities will be estimated using the Kaplan-Meier method.

Expected accrual is estimated at 2 patient/month with total duration of the study estimated 38 months.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.



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During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (<http://ppr/>). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

N/A

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated..

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet: <http://mskweb2.mskcc.org/irb/index.htm>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol



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monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

Informed consent will be obtained from all research subjects. The informed consent document will explain to the subjects the risks, benefits, toxicities/side effects, alternatives/options for treatment, and financial costs/burdens. Participation in the study is voluntary. The study drug will be provided commercially by Pfizer at no cost to the patient. Patients will be billed for patient care services.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- x Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- x Medical record number
- x Disease/histology (if applicable)
- x Protocol number and title

Data needing to be entered:

- x The date the adverse event occurred
- x The adverse event
- x Relationship of the adverse event to the treatment (drug, device, or intervention)
- x If the AE was expected
- x The severity of the AE
- x The intervention

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- x Detailed text that includes the following
 - o A explanation of how the AE was handled
 - o A description of the subject's condition
 - o Indication if the subject remains on the study
 - o If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 Adverse Event Reporting

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see Section 17.2.2 requiring immediate notification to Pfizer or its designated representative.) For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Serious adverse events require immediate notification to Pfizer or its designated representative beginning from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the clinical trial, ie, prior to undergoing any trial-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

Adverse events serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of trial treatment through last subject visit. If a patient begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

Serious Adverse Event Contact Information

All serious adverse events regardless of treatment group or suspected relationship to study drug must be reported immediately by fax to the number listed below:

TOLL FREE NUMBER: (866) 997-8322.

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17.2.2 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation;
- Exposure in utero.

Worsening of signs and symptoms of the malignancy under trial should be reported as adverse events in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study should not be reported as a serious adverse event (SAE) unless the outcome is fatal within the safety reporting period. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be



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recorded as an adverse event and as a SAE with CTCAE grade 5. Hospitalizations clearly due to signs and symptoms of disease progression should not be reported as SAEs.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.



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If required on the adverse event case report forms, the investigator will use the following definitions of severity in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 to describe the maximum intensity of the adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event report.

GRADE Clinical Description of Severity

- 0 No Change from Normal or Reference Range (This grade is not included in the Version 3.0 document but may be used in certain circumstances.)
- 1 MILD Adverse Event
- 2 MODERATE Adverse Event
- 3 SEVERE Adverse Event
- 4 LIFE-THREATENING OR DISABLING Adverse Event
- 5 DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records. In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

For investigational products within clinical trials and for marketed products, an exposure in-utero (EIU) occurs if:

- 1) a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
- 2) a male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial subject or trial subject's partner becomes or is found to be pregnant during the trial subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (e.g. a nurse reports that she is

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pregnant and has been exposed to a cytotoxic product by inhalation or adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy). Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page. When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, each trial subject will be questioned about adverse events.

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local regulations, as appropriate. All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports. In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses

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must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

For tumor screening testing, the patient may consent by fax and, if found eligible, will re-consent in person prior to trial initiation.

19.0 REFERENCES

Dickson, MA, Tap WD, Keohan MK, et al. Phase II Trial of the CDK4 inhibitor PD0332991 in Patients with Advanced CDK4-amplified Well-Differentiated or Dedifferentiated Liposarcoma. J Clin Onc, 2013, in press.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

Karpeh MS, Brennan MF, Cance WG, et al. Altered patterns of retinoblastoma gene product expression in adult soft-tissue sarcomas. Br J Cancer. 1995;72:986-991.

Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue

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sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol*. 2007;25:3144-3150.

Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol*. 2007;25:2755-2763.

O'Dwyer P, LoRusso P, DeMichele A, et al. A phase I dose escalation trial of a daily oral CDK 4/6 inhibitor PD-0332991 *J Clin Oncol* 2007;25:Abstr 3550.

Singer S, Socci ND, Ambrosini G, et al. Gene expression profiling of liposarcoma identifies distinct biological types/subtypes and potential therapeutic targets in well-differentiated and dedifferentiated liposarcoma. *Cancer Res*. 2007;67:6626-6636.

Sirvent N, Coindre JM, Maire G, et al. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. *Am J Surg Pathol*. 2007;31:1476-1489.

Van Glabbeke M, Verweij J, Judson I, Nielsen OS. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. *Eur J Cancer*. 2002;38:543-549.

Vaughn DJ, Flaherty K, Lal P, et al. Treatment of growing teratoma syndrome. *N Engl J Med*. 2009;360:423-424.

20.0 APPENDICES



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IRB PROTOCOL

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10-094: A Phase II Study of Palbociclib in Patients with Advanced or Metastatic Liposarcoma

PATIENT MEDICATION LOG FOR Palbociclib 2/1 schedule

NAME: _____ MRN: _____ CYCLE: _____ WEEK: _____

Number of Pills given: _____ Number of Pills Returned: _____

Pill Bottle (s) returned: Circle Yes or No Total Daily Dose: _____

Day #	Date	Time Dose Taken	Taken with food (Yes or No)	Please Circle One	# of Capsules Taken
1				A.M P.M	
2				A.M P.M	
3				A.M P.M	
4				A.M P.M	
5				A.M P.M	
6				A.M P.M	
7				A.M P.M	
8				A.M P.M	
9				A.M P.M	
10				A.M P.M	
11				A.M P.M	
12				A.M P.M	
13				A.M P.M	
14				A.M P.M	

INSTRUCTIONS: Please remember to take medication with food. This log should be filled in each time you take any medication at home and returned upon your next clinic visit or when the form is completed.

Patient Signature: _____ **Date:** _____

*The patient states he/she has taken the medication as documented above.

Consenting Professional/RN Signature: _____ **Date:** _____

Consenting Professional/RN Comments:



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10-094: A Phase II Study of Palbociclib in Patients with Advanced or Metastatic Liposarcoma

PATIENT MEDICATION LOG FOR Palbociclib 3/1 schedule

NAME: _____ MRN: _____ CYCLE: _____ WEEK: _____

Number of Pills given: _____ Number of Pills Returned: _____

Pill Bottle (s) returned: Circle Yes or No Total Daily Dose: _____

Day #	Date	Time Dose Taken	Taken with food (Yes or No)	Please Circle One	# of Capsules Taken
1				A.M P.M	
2				A.M P.M	
3				A.M P.M	
4				A.M P.M	
5				A.M P.M	
6				A.M P.M	
7				A.M P.M	
8				A.M P.M	
9				A.M P.M	
10				A.M P.M	
11				A.M P.M	
12				A.M P.M	
13				A.M P.M	
14				A.M P.M	
15				A.M P.M	
16				A.M P.M	
17				A.M P.M	
18				A.M P.M	



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Day #	Date	Time Dose Taken	Taken with food (Yes or No)	Please Circle One	# of Capsules Taken
19				A.M P.M	
20				A.M P.M	
21				A.M P.M	

INSTRUCTIONS: Please remember to take medication with food. This log should be filled in each time you take any medication at home and returned upon your next clinic visit or when the form is completed.

Patient Signature: _____ **Date:** _____

*The patient states he/she has taken the medication as documented above.

Consenting Professional/RN Signature: _____ **Date:** _____

Consenting Professional/RN Comments:



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APPENDIX B LIST OF CYP3A4 INHIBITORS AND INDUCERS

CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan Lovastatin	Progesterone
Amiodarone	Diltiazem	Mefloquine	Propofol
Amlodipine	Disulfiram	Mestranol	Propoxyphene
Amprenavir	Docetaxel	Methadone	Quinidine
Anastrozole	Doxorubicin	Methimazole	Quinine
Aprepitant	Doxycycline	Methoxsalen	Quinupristin
Atazanavir	Drospirenone	Methylprednisolone	Rabeprazole
Atorvastatin	Efavirenz	Metronidazole	Ranolazine
Azelastine	Enoxacin	Miconazole	Risperidone
Azithromycin	Entacapone	Midazolam	Ritonavir
Betamethasone	Ergotamine	Mifepristone	Saquinavir
Bortezomib	Erythromycin	Mirtazapine	Selegiline
Bromocriptine	Ethinyl estradiol	Mitoxantrone	Sertraline
Caffeine	Etoposide	Modafinil	Sildenafil
Cerivastatin	Felodipine	Nefazodone	Sirolimus
Chloramphenicol	Fentanyl	Nelfinavir	Sulconazole
Chlorzoxazone	Fluconazole	Nevirapine	Tacrolimus
Cimetidine	Fluoxetine	Nicardipine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nifedipine	Telithromycin
Cisapride	Fluvoxamine	Nisoldipine	Teniposide
Clarithromycin	Fosamprenavir	Nizatidine	Testosterone
Clemastine	Glyburide	Norfloxacin	Tetracycline
Clofazimine	Grapefruit juice (2)	Olanzapine	Ticlopidine
Clotrimazole	Haloperidol	Omeprazole	Tranylcypromine
Clozapine	Hydralazine	Orphenadrine	Trazodone
Cocaine	Ifosfamide	Oxybutynin	Troleandomycin
Conivaptan	Imatinib	Paroxetine	Valproic acid
Cyclophosphamide	Indinavir	Pentamidine	Venlafaxine
Cyclosporine	Irbesartan	Pergolide	Verapamil
Danazol	Isoniazid	Phencyclidine	Vinblastine
Dasatinib (1)	Isradipine	Pilocarpine	Vincristine
Delavirdine	Itraconazole	Pimozide	Vinorelbine
Desipramine	Ketoconazole	Pravastatin	Voriconazole
Dexmedetomidine	Lansoprazole	Prednisolone	Zafitukast
Diazepam	Lidocaine		Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

When Palbociclib is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of Palbociclib is the potential outcome. The co-administration of 'inducers' would potentially lower plasma Palbociclib concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed.

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at

<http://medicine.iupui.edu/flockhart/>.



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Appendix C

ECOG		KARNOFSKY	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead